REMARKS

Claims 1, 2, 18, 19, 23-36, and 46-59 are pending in the present application. Claims 1, 23, 46, and 49-52 have been amended to more particularly point out the invention. Claim 46 has been amended as per the Examiner's suggestion. Support for the amendments to claims 1 and 49-52 can be found in the specification. Support for the amendments to claims 1, 49, and 52 can be found in the specification, e.g., at page 9, lines 29-31, and page 11, lines 21-page 12, line 14. Support for the amendments to claims 50 and 51 can be found, e.g., at page 9, lines 29-31; and page 11, lines 21-page 12, line 14; and at page 53, lines 16-17. Thus, the amendments to claims 1 and 49-52 do not introduce new matter.

The Invention

The claimed invention provides screening methods for the identification of compounds that can be used to treat neuronal disorders and disorders involving excitotoxicity, as well as methods of screening for compounds that modify the level of expression or activity of JNK3. The application discloses that mice lacking functional JNK3 genes are resistant to excitotoxic damage and that JNK3 is a mediator of kainate/glutamate induced excitotoxicity. Thus, JNK3 is a target for limiting or preventing excitotoxic damage. As a result, reducing JNK3 activity and/or expression protects neurons from cell death.

35 U.S.C. § 112, Second Paragraph

Claim 46 and claim 47 which depends from claim 46 have been rejected as allegedly indefinite. To expedite prosecution, applicants have amended claim 46 as suggested in the Office Action, to recite "phosphorylation in the presence of the compound compared to the phosphorylation in the absence of the compound; and..." The rejection under 35 U.S.C. § 112, second paragraph, is therefore moot with respect to claim 46 and applicants request that the rejection be withdrawn. By virtue of its dependency from claim 46, the rejection of claim 47 should also be withdrawn.

Claims 50 and 51 have also been rejected as allegedly indefinite for use of the phrase "allow the interaction of." Applicants respectfully disagree.

In response, applicants note that the skilled artisan would understand the term "interaction" in the context of an enzyme and its substrate to mean that the enzyme acts on its substrate, e.g., by binding to cause a change in the substrate. One of skill in the art would appreciate that such an interaction can be measured by determining a physical interaction between the enzyme and its substrate (e.g., binding) or by determining an enzymatic interaction between the enzyme and its substrate, e.g., phosphorylation of the substrate. The Office Action has not provided any suggestion for alternative interpretations of the phrase that would render the term indefinite. Applicants, therefore believe that claims 50 and 51 are definite and respectfully request that the rejection of claims 50 and 51 under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 103 (a)

Claims 1, 2, 18, and 19 have been rejected as allegedly obvious over McKay et al., U.S. Patent No. 5,877,309 ("McKay"). Applicants respectfully disagree with the rejection. However, to advance prosecution, applicants have amended claim 1 to recite that the cell that can express JNK3 is a neuronal cell. Claims 2, 18, and 19 include this limitation by virtue of their dependencies from claim 1.

As the Examiner is no doubt aware, the MPEP states (at § 2142):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). [Emphasis added]

and at § 2143.03:

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

McKay does not disclose or suggest the use of neuronal cells for methods of assaying modulation of expression of JNK protein as is required by claims 1, 2, 18, and 19. The cell line used by McKay is a human lung carcinoma cell line A549, not a neuronal cell line, and McKay is primarily concerned with diagnosis and therapy of tumor formation and metastasis. The Office Action does not point to any suggestion or motivation in McKay to use neuronal cells for identifying modulators of JNK expression, nor does McKay mention neuronal disorders. Since McKay does not disclose the use of neuronal cells or suggest their use, not all of the claim elements are taught in the reference and the Office Action does not establish a *prima facie* case of obviousness.

The Office Action (at page 4, first full paragraph) states

> using the reference of McKay et al. it would have been obvious to one of ordinary skill in the art, especially those interested in identifying agents other than oligonucleotides, to identify small organic compounds, peptides or peptidomimetics or inorganic compounds that modulate the expression of JNK3. One of ordinary skill in the art would have been motivated to do so in view of common knowledge in the art that the oligonucleotides used as antisense is not always successful or even economical or simply to have an extensive list of compounds that could be easy to manufacture, pack, and deliver and or administer to a patient.

Applicants maintain that the present invention is neither disclosed nor suggested by McKay. McKay describes a method for assaying the effect of antisense oligonucleotides on the expression of JNK proteins. This is distinct from the present invention, in which peptides, peptidomimetics, small organic molecules, or small inorganic molecules are screened for their

effect on the expression of a JNK gene. The Office Action offers only an opinion as to what one in the art would believe about antisense oligonucleotides without providing any support for the opinion. "The rational supporting an obviousness rejection may be based on common knowledge in the art or 'well-known' prior art" (MPEP at § 2144.03). The Office Action merely states that it "would have been obvious to one in the art [to use agents other than antisense oligonucleotides]." This does not meet the standard for supporting an obviousness rejection. The Office Action merely offers an opinion as to the lack of success of using antisense (even though McKay reports using it successfully) as well as opinion regarding commercial aspects of using antisense oligonucleotides. Even if the comments in the Office Action regarding the use of antisense oligonucleotides were true, the Office Action proffers merely the unsupported opinion that one in the art would turn to peptides, peptidomimetics, small organic molecules, or small inorganic molecules. Nothing is provided in the Office Action or in the cited prior art to show that these opinions are based on common knowledge in the art or on well-known prior art. More importantly, the reasons alleged to support modifying McKay are generic, i.e., they are in no way related to the cited prior art, but are merely citations of applicants' claim elements. There is simply no suggestion in the cited art for making the changes the Examiner asserts. Applicants respectfully request that if the rejection is maintained that the Examiner provide support for the opinions put forth in the Office Action.

Claims 49-59 have been rejected under 35 U.S.C. 103 (a), as allegedly obvious over Gupta et al. (1996, EMBO Journal Vol. 15(11):2760-2770; "Gupta") and McKay et al. (U.S. Patent No. 5,877,309). Applicants respectfully disagree.

Amended claims 49-52 recite the use of neuronal cells and amended claims 51 and 52 recite that JNK be expressed and isolated from a neuronal cell. Claims 53-59 include this limitation by virtue of their dependencies from claims 49, 50, 51, or 52. Neither Gupta nor McKay describe the identification of modulators of JNK activity in neuronal cells. As discussed above, all claim limitations must be found in the prior art reference(s) to make the claimed invention obvious. Applicants assert that neither Gupta nor McKay disclose testing compounds for their ability to modulate JNK activity in neuronal cells. McKay recites a method of testing antisense oligonucleotides for their ability to modulate the expression of a JNK protein. Gupta describes measuring the kinase activity of recombinant JNK expressed in and isolated from

Chinese hamster ovary (CHO) cells. In contrast, the present claims recite a neuronal cell capable of expressing JNK3 and JNK3 expressed and isolated from a neuronal cell, respectively. CHO cells are not neuronal cells; therefore, the prior art references do not describe or suggest all the claim limitations.

In view of the amendments to the claims and the arguments presented above, applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103 (a).

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment. Applicants point out that a supplemental Information Disclosure Statement/Form 1449 was filed for this application on December 3, 2002, reporting art cited by a foreign patent office in a corresponding foreign application.

Applicants believe the claims are in condition for allowance, which action is respectfully requested. Enclosed is a $460.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 10363-005001.

Respectfully submitted,

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Lisa N. Geller, Ph.D., J.D.
Reg. No. 51,726

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 1, 23, 46, and 49-52 have been amended as follows. For convenience, all of the pending claims are provided.

1. (Twice amended) A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a neuronal cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell; and

comparing the amount of JNK3 expression in the presence and absence of the compound, wherein a difference in the level of expression indicates that the compound modulates JNK3 expression.

2. (Reiterated) The method of claim 1, wherein the compound decreases the expression of JNK3.

18. (Reiterated) The method of claim 1, wherein the compound is a soluble peptide.

19. (Reiterated) The method of claim 1, wherein the compound is a phosphopeptide.

23. (Reiterated) A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell;

comparing the amount of JNK3 expression in the presence and absence of the compound;

selecting the compound if there is a difference in the level of expression in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the compound modulates JNK3 expression.

24. (Reiterated) The method of claim 23, wherein the compound decreases the expression of JNK3.

25. (Reiterated) The method of claim 23, wherein the animal model is a mouse model.

26. (Reiterated) The method of claim 23, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

27. (Reiterated) A method of identifying a compound that modulates JNK3 activity, the method comprising:

incubating a cell that exhibits JNK3 activity with a compound under conditions and for a time sufficient for the cell to exhibit JNK3 activity absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 activity in the cell in the presence of the compound;

measuring JNK3 activity in the control cell;

comparing the amount of JNK3 activity in the presence and absence of the compound;

selecting the compound if there is a difference in the level of activity in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity, wherein a decrease in excitoxicity in the animal indicates that the compound modulates JNK3 activity.

28. (Reiterated) The method of claim 27, wherein the animal model is a mouse model.

29. (Reiterated) The method of claim 27, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

30. (Reiterated) The method of claim 27, wherein the compound decreases JNK3 activity.

31. (Reiterated) The method of claim 27, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

32. (Reiterated) A method of identifying a compound that modulates the binding of a JNK3 polypeptide to a substrate, the method comprising:

comparing the amount of a JNK3 polypeptide bound to a substrate in the presence and absence of a compound;

selecting the compound if there is a difference in the amount of JNK3 polypeptide bound to the substrate in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the selected compound modulates the binding of a JNK3 polypeptide to the substrate.

33. (Reiterated) The method of claim 32, wherein the animal model is a mouse model.

34. (Reiterated) The method of claim 32, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

35. (Reiterated) The method of claim 32, wherein the binding of a JNK3 polypeptide to a substrate is decreased.

36. (Reiterated) The method of claim 32, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

46. A method of identifying a compound that inhibits phosphorylation of a JNK3 substrate, the method comprising:

comparing the amount of a JNK3 substrate phosphorylated in the presence compared to the absence of a compound;

selecting the compound if there is a decrease in the amount of JNK3 substrate phosphorylation in the presence [compared to] of the compound compared to phosphorylation in the absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder [and assaying the animal for] to assess excitotoxicity,

wherein a decrease in excitotoxicity [in the animal] indicates that the selected compound inhibits the phosphorylation of a JNK3 substrate.

47. (Reiterated) The method of claim 46, wherein the JNK3 substrate is c-Jun.

48. (Reiterated) The method of claim 23, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule.

49. (Amended) A method of identifying a candidate compound for the treatment of a disorder related to excitotoxicity, the method comprising:

incubating a neuronal cell that can express a JNK3 protein with a compound under conditions sufficient to express the JNK3 protein;

incubating a control cell under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a disorder related to excitotoxicity.

50. (Amended) A method of identifying a candidate compound for the treatment of a disorder related to excitotoxicity, the method comprising:

incubating a JNK3 protein <u>expressed and isolated from a neuronal cell</u> with a JNK3 substrate and a compound under conditions sufficient to allow the interaction of the JNK3 protein with a JNK3 substrate;

incubating the JNK3 protein and the JNK3 substrate under the same conditions and for the same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a disorder related to excitotoxicity.

51. (Amended) A method of identifying a candidate compound for the treatment of a neuronal disorder, the method comprising:

incubating a JNK3 protein <u>expressed and isolated from a neuronal cell</u> with a JNK3 substrate and a compound under conditions sufficient to allow the interaction of the JNK3 protein with the JNK3 substrate;

incubating the JNK3 protein and the JNK3 substrate under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a neuronal disorder.

52. (Amended) A method of identifying a candidate compound for the treatment of a neuronal disorder, the method comprising:

incubating a neuronal cell that can express a JNK3 protein with a compound under conditions sufficient to express the JNK3 protein;

incubating a control cell under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a neuronal disorder.

53. (Reiterated) The method of claim 49, 50, 51, or 52, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule.

54. (Reiterated) The method of claim 49, 50, 51, or 52, wherein the compound inhibits the ability of JNK3 to phosphorylate a substrate.

55. (Reiterated) The method of claim 54, wherein the substrate is c-Jun.

56. (Reiterated) The method of claim 49, 50, 51, or 52, wherein the compound inhibits the ability of JNK3 to bind a substrate.

57. (Reiterated) The method of claim 56, wherein the substrate is c-Jun.

58. (Reiterated) The method of claim 49 or 50, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

59. (Reiterated) The method of claim 49, 50, 51, or 52, wherein the disorder is a seizure disorder, epilepsy, cerebrovascular disorder, ischemia, spinal cord injury, spinal cord pressure, dementia, Alzheimer's disease, Parkinson's disease, a neurogenerative disorder, Huntington disease, or motoneuron disease.